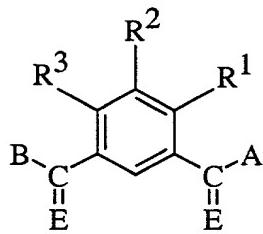


CLAIMS

What is claimed is:

1. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering to the mammal an MMP inhibiting amount of a compound of Formula I



wherein:

R¹, R², and R³ independently are hydrogen, halo, hydroxy, C₁-C₆ alkyl,

C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃;

10 E is independently O or S;

A and B independently are OR⁴ or NR⁴R⁵;

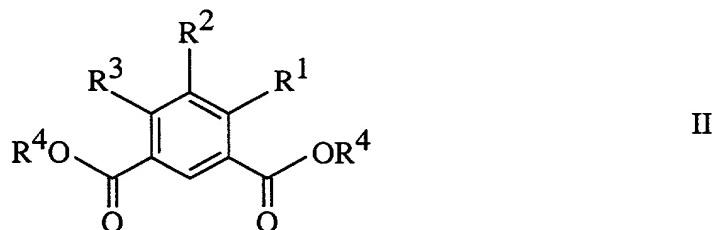
each R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴

15 and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring, optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted;

n is an integer from 0 to 6;

20 or a pharmaceutically acceptable salt thereof.

2. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering to the mammal an MMP inhibiting amount of a compound of Formula II



5

wherein:

R¹, R², and R³ independently are hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃; and

R⁴ and R⁵ is independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆

10 alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, or (CH₂)_n heteroaryl, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring, optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted;

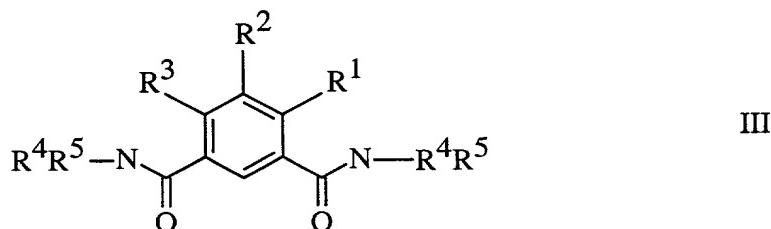
15

n is an integer from 0 to 6;

or a pharmaceutically acceptable salt thereof.

3. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering to the mammal an MMP inhibiting amount of a compound of Formula III

20



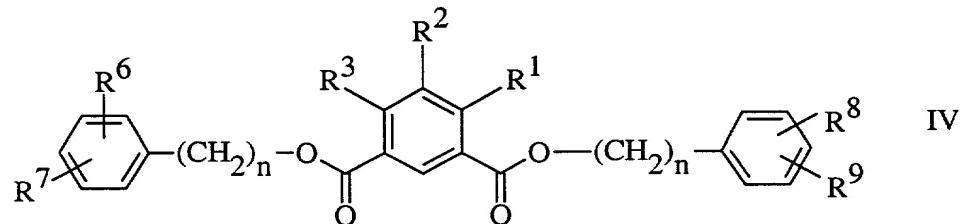
wherein:

R¹, R², and R³ independently are hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃;

R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring, optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted;

10 n is an integer from 0 to 6;
or a pharmaceutically acceptable salt thereof.

4. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering to the mammal an MMP inhibiting amount of a compound of Formula IV



wherein:

Each R¹, R², and R³ independently are hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃;

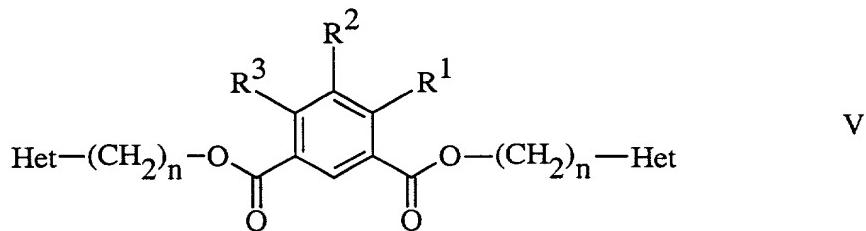
20 Each R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring, optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted;

R⁶, R⁷, R⁸, and R⁹ independently are hydrogen, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, nitro, or NH₂; and

n is an integer from 0 to 6;

or a pharmaceutically acceptable salt thereof.

- 5 5. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering to the mammal an MMP inhibiting amount of a compound of Formula V



wherein:

- 10 R¹, R², and R³ independently are hydrogen, halo, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN, or CF₃, and Het is an unsubstituted or substituted heteroaryl group;

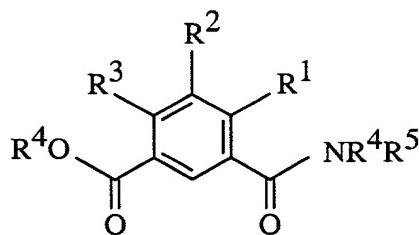
R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (CH₂)_n aryl, (CH₂)_n cycloalkyl, (CH₂)_n heteroaryl, or R⁴

- 15 and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring, optionally containing a heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted;

n is an integer from 0 to 6;

- 20 or a pharmaceutically acceptable salt thereof.

6. A method for inhibiting matrix metalloproteinase enzymes in a mammal comprising administering to the mammal an MMP inhibiting amount of a compound of Formula VI



VI

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 , R^2 , and R^3 independently are hydrogen, halo, hydroxy, C₁-C₆ alkyl,

5 C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NO₂, NR⁴R⁵, CN,
or CF₃;

R⁴ and R⁵ independently are H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆

alkynyl, $(\text{CH}_2)_n$ aryl, $(\text{CH}_2)_n$ cycloalkyl, $(\text{CH}_2)_n$ heteroaryl, or R^4

and R⁵ when taken together with the nitrogen to which they are

attached complete a 3- to 8-membered ring, optionally containing heteroatom selected from O, S, or NH, and optionally substituted or unsubstituted; and

n is an integer from 0 to 6.

7. A compound selected from:

15 4-Methoxy-N,N'-bis-(4-methoxybenzyl)-isophthalamide;

Isophthalic acid di-(2,1,3-benzothiadiazol-5-yl) methyl ester;

4-Methoxy-isophthalic acid dibenzyl ester;

4-Methoxy-isophthalic acid dipyrindin-4-ylmethyl ester;

Isophthalic acid bis-(4-fluoro-benzyl) ester;

Isophthalic acid bis-(3-fluoro-benzyl) ester;

Isophthalic acid bis-(4-methoxy-benzyl) ester;

Isophthalic acid bis-(3-methoxy-benzyl) ester;

Isophthalic acid bis-(1,3-benzodioxol-5-ylmethyl) ester;

N,N'-Bis-(3-fluoro-benzyl)-isophthalamide;

25 4-Acetyl-isophthalic acid dibenzyl ester;

4-Methoxycarbonylmethoxy-isophthalic acid dibenzyl ester;

- N,N'-Bis-1,3-benzodioxol-5-ylmethyl-4-methoxy-isophthalamide;
N-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N'-(4-methoxy-benzyl)-
isophthalamide;
4-Methoxy-N,N'-bis-(4-methoxy-benzyl)-isophthalamide;
5 N-1,3-Benzodioxol-5-ylmethyl-N'-(4-chloro-benzyl)-4-methoxy-
isophthalamide;
N-Benzyl-4-methoxy-N'-(4-methoxy-benzyl)-isophthalamide;
N'-Benzyl-4-methoxy-N-(4-methoxy-benzyl)-isophthalamide;
4-Methoxy-N-(4-methoxy-benzyl)-N'-pyridin-4-ylmethyl-isophthalamide;
N'-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N-(2-phenoxy-ethyl)-
isophthalamide;
N-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N'-(2-phenoxy-ethyl)-
isophthalamide;
N-1,3-Benzodioxol-5-ylmethyl-N'-furan-2-ylmethyl-isophthalamide;
15 N'-1,3-Benzodioxol-5-ylmethyl-N-(2-ethoxy-ethyl)-4-methoxy-
isophthalamide;
N,N'-Bis-(3-hydroxymethyl-phenyl)-isophthalamide;
N-Benzyl-4-methoxy-N'-(2-phenoxy-ethyl)-isophthalamide;
4-Methoxy-N,N'-bis-(4-methyl-benzyl)-isophthalamide;
20 4-Methoxy-N,N'-bis-(3-methoxy-benzyl)-isophthalamide;
N-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N'-(4-methoxy-benzyl)-
isophthalamide;
N-1,3-Benzodioxol-5-ylmethyl-isophthalamic acid,
(4-carboxyphenyl)methyl ester;
25 4-{{[3-(3-Methoxy-benzylcarbamoyl)-benzoylamino]-methyl}-benzoic
acid;
4-Methoxy-isophthalic acid di-2,1,3-benzothiadiazol-5-ylmethyl ester;
4-{{[3-(3-Methoxy-benzylcarbamoyl)-benzoylamino]-methyl}-benzoic acid
methyl ester;
30 N-(3-Methoxy-benzyl)-N'-(4-nitro-benzyl)-isophthalamide;
N-(3,4-Dichloro-benzyl)-N'-pyridin-4-ylmethyl-isophthalamide;

N1,N3-Bis-1,3-benzodioxol-5-ylmethyl-4-ethoxy-isophthalamide;
N-(4-Chloro-benzyl)-N'-(3-methoxy-benzyl)-isophthalamide;
N-(3,4-Dichloro-benzyl)-N'-(3-methoxy-benzyl)-isophthalamide;
N-(4-Methoxy-benzyl)-N'-(3-methoxy-benzyl)-isophthalamide;
5 N,N'-Bis-(4-fluoro-3-methoxy-benzyl)-isophthalamide;
4-Ethoxy-N1,N3-bis-(3-methoxy-benzyl)-isophthalamide;
N1,N3-Bis-1,3-benzodioxol-5-ylmethyl-4-ethoxy-isophthalamide;
N-(3-Methoxy-benzyl)-N'-pyridin-3-ylmethyl-isophthalamide;
N-(3-Methoxy-benzyl)-N'-pyridin-4-ylmethyl-isophthalamide;
10 N1-1,3-Benzodioxol-5-ylmethyl-N3-pyridin-3-ylmethyl-isophthalamide;
N-(3-Methoxy-benzyl)-N'-(3-trifluoromethoxy-benzyl)-isophthalamide;
N1,N3-Bis-1,3-benzodioxol-5-ylmethyl-4-isopropoxy-isophthalamide;
4-Isopropoxy-N1,N3-bis-(3-methoxy-benzyl)-isophthalamide;
N1-Benzyl-4-methoxy-N3-(4-methoxy-benzyl)-isophthalamide;
15 N1-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N3-(4-methoxy-benzyl)-
isophthalamide;
N1-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N3-(2-phenoxy-ethyl)-
isophthalamide;
N1-Benzyl-4-methoxy-N3-(2-phenoxy-ethyl)-isophthalamide;
20 N1-1,3-Benzodioxol-5-ylmethyl-N3-(4-chloro-benzyl)-4-methoxy-
isophthalamide;
N3-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N1-(4-methoxy-benzyl)-
isophthalamide;
N3-Benzyl-4-methoxy-N1-(4-methoxy-benzyl)-isophthalamide;
25 N3-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N1-(2-phenoxy-ethyl)-
isophthalamide;
N3-1,3-Benzodioxol-5-ylmethyl-N1-(2-ethoxy-ethyl)-4-methoxy-
isophthalamide;
4-Methoxy-N1-(4-methoxy-benzyl)-N3-pyridin-4-ylmethyl-
30 isophthalamide;
4-Amino-N1,N3-bis-1,3-benzodioxol-5-ylmethyl-isophthalamide;
4-Acetylamino-N1,N3-bis-1,3-benzodioxol-5-ylmethyl-isophthalamide;

- N-(3-Methoxy-benzyl)-N'-pyridin-3-ylmethyl-isophthalamide;
N-(3-Methoxy-benzyl)-N'-pyridin-4-ylmethyl-isophthalamide;
N1-1,3-Benzodioxol-5-ylmethyl-N3-pyridin-3-ylmethyl-isophthalamide;
N-(4-Chloro-benzyl)-N'-(3-methoxy-benzyl)-isophthalamide;
5 N-(3,4-Dichloro-benzyl)-N'-(3-methoxy-benzyl)-isophthalamide;
N-(4-Methoxy-benzyl)-N'-(3-methoxy-benzyl)-isophthalamide;
N-(3-Methoxy-benzyl)-N'-(4-methyl-benzyl)-isophthalamide;
N,N'-Bis-(4-fluoro-3-methoxy-benzyl)-isophthalamide;
({3-[1,3-Benzodioxol-5-ylmethyl]-carbamoyl}-benzoyl}-benzyl-amino)-
10 acetic acid;
N-Benzo[1,3]dioxol-5-ylmethyl-isophthalamic(4-hydroxymethyl-benzoic
acid) ester;
N-(3,4-Dichloro-benzyl)-N'-pyridin-4-ylmethyl-isophthalamide;
N-(3-Methoxy-benzyl)-N'-(4-nitro-benzyl)-isophthalamide;
15 4-{[3-(3-Methoxy-benzylcarbamoyl)-benzoylamino]-methyl}-benzoic acid
methyl ester;
N-3-methoxybenzyl-isophthalamic(4-hydroxymethyl-benzoic acid) ester;
4-{[3-(3-Methoxy-benzylcarbamoyl)-benzoylamino]-methyl}-benzoic
acid;
20 N-(3-Amino-benzyl)-N'-(3-methoxy-benzyl)-isophthalamide;
N-(3-Methoxy-benzyl)-N'-(3-nitro-benzyl)-isophthalamide;
4-Ethoxy-N'1,N''3-bis-(3-methoxy-benzyl)-isophthalamide;
N1,N3-Bis-1,3-benzodioxol-5-ylmethyl-4-ethoxy-isophthalamide;
25 N1,N3-Bis-1,3-benzodioxol-5-ylmethyl-4-propoxy-isophthalamide;
N1,N3-Bis-1,3-benzodioxol-5-ylmethyl-4-isopropoxy-isophthalamide;
N1,N3-Bis-2,1,3-benzothiadiazol-5-ylmethyl-4-methoxy-isophthalamide;
and
4-Methoxy-isophthalic acid di-2,1,3-benzothiadiazol-5-ylmethyl ester.

8. A pharmaceutical composition, comprising a compound of Claim 1, or a
30 pharmaceutically acceptable salt thereof, admixed with a pharmaceutically
acceptable carrier, diluent, or excipient.

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- 5
9. A pharmaceutical composition for inhibiting MMP-13 in a mammal, comprising an MMP-13 inhibiting amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, diluent, or excipient.
- 10
10. A method for inhibiting MMP-13 in an animal, comprising administering to the animal an MMP-13 inhibiting amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.
11. A method for treating a disease mediated by an MMP-13 enzyme, comprising administering to a patient suffering from such a disease an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.
- 15
12. A method for treating a cancer, comprising administering to a patient suffering from such a disease an anticancer effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.
- 20
13. A method for treating breast carcinoma, comprising administering to a patient suffering from such a disease an anticancer effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.
- 25
14. A method for treating a rheumatoid arthritis, comprising administering to a patient suffering from such a disease an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.
- 30
15. A method for treating a osteoarthritis, comprising administering to a patient suffering from such a disease an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

16. A method for treating a heart failure, comprising administering to a patient suffering from such a disease an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

- 5 17. A method for treating a inflammation, comprising administering to a patient suffering from such a disease an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.